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Any Genetic Epilepsy with Tonic-Clonic Seizures Carries the Risk of SUDEP

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LETTER TO THE EDITOR

We read with interest the article by Bagnall et al. on a 24 year-old male with nonlesional, bitemporal lobe epilepsy, who reportedly died of sudden unexpected death in epilepsy (SUDEP) approximately 12 hours after the last witnessed tonic-clonic seizure [Bouratzis, V. *et al*., 2023]. At the time of SUDEP, he was on anti-seizure drug (ASD) therapy with levetiracetam (1500 mg/d), lamotrigine (400 mg/d), and clobazam (10mg/d) [Bouratzis, V. *et al*., 2023]. Post mortem genetic studies revealed a variant in the *KNCH2* gene that was held responsible for SUDEP in the reported patient [Bouratzis, V. *et al*., 2023]. The study is excellent but raises concerns that should be discussed.

We disagree that the index patient died of SUDEP. Variants in *HCNH2* have been associated not only with SUDEP but also with long-QT syndrome, which can be complicated by sudden cardiac death (SCD) [Wei, L. *et al*., 2023]. Therefore, it cannot be ruled out that the patient died from asystole, ventricular tachycardia, or ventricular fibrillation. We should know if the family history was positive for SCD and if any of the witnessed seizures were in fact a convulsive syncope due to ventricular arrhythmias. Has the patient ever been subjected to video-EG monitoring? Have long-term ECG recordings been carried out?

A second limitation is that apart from the index patient, no other family members with a history of seizures have had genetic testing. Knowing whether the variant occurred sporadically in the index patient or was inherited is important not only for assessing phenotypic heterogeneity and disease progression but also for genetic counselling of living family members.

A third limitation of the study is that the number of mutated genes associated with SUDEP is incomplete. In general, SUDEP can occur after tonic-clonic seizures in isolated genetic epilepsies and non-isolated genetic epilepsies that appear as one of other phenotypic features of syndromic or non-syndromic genetic disorders. Mutated genes associated with isolated genetic epilepsies include *SCN1A, SCN8A, SCN1B, SCN2A, STXBP1, SCN8A, HCN1, HCN2, HCN4, GNB5, KCNA1, KCNT1, DEPDC5, NPRL2, NPRL3, CSTB, TSC1, TSC2, LIG1, CHNRA4, CHNRA2, KCNQ2, KCNQ3, SCN2B, GABRG2, GABRA1, CACNB4, CLCN2*, and *EFHC1* [Steinlein, O. K. *et al*., 2008]. Non-isolated epilepsies manifesting with tonic-clonic seizures occur in mitochondrial disorders (MIDs) which can be syndromic (e.g. MELAS, MERRF, Leigh syndrome, NARP, Alpers-Huttenlocher syndrome, MNGIE due to *LIG3* variants, mitochondrial depletion syndrome) or non-syndromic. Other genetic metabolic disorders associated with epilepsy include beta-oxidation defects, amino acid disorders, cofactor-related metabolic diseases, purine and pyrimidine metabolic diseases, congenital disorders of glycosylation, and lysosomal and peroxisomal disorders [Almannai, M. *et al*., 2021]. SUDEP may also occur in patients with spinocerebellar ataxias with epilepsy (e.g. SCA13, SCA17, SCA10, SCA8, SCA2), hereditary spastic paraplegias with epilepsy (e.g. SPG4, SPG6, SPG18, SPG35, SPG47), and various unclassified syndromes with epilepsy (e.g. Harel-Yoon syndrome, neonatal rigidity and multifocal seizure (RMFSL) syndrome, *SLC25A19*-related thiamine metabolism dysfunction, hyperinsulinism / hyperammonemia syndrome, glutaminase hyperactivity). Several genetic heart disorders are associated with epilepsy (e.g. long-QT syndrome due to *KCNQ1, KCNH2, SCN5A, NOS1AP, KCNE1, ANK2, AKAP9*, Brugada syndrome due to *SCN5A, HCN4, SCN1B, CACNAB2,* arrhythmogenic right ventricular cardiomyopathy due to *DSC2, DSG2, RYR2, DSP*, familial sinus bradycardia syndrome due to *HCN1, HCN2, HCN4, or d*ilated cardiomyopathy due to mutated

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MYH6, LDB3, DMD, or MYBPC3). Also not discussed were leucodystrophies, lipofuscinoses, gangliosidoses (Gaucher disease, Tay Sachs disease, or complex hereditary neuropathies). There are numerous chromosomal defects which are associated with epilepsy (e.g. Wolf–Hirschhorn (4p-) syndrome, Miller–Dieker syndrome, Angelman syndrome, the inversion duplication 15 syndrome, terminal deletions of chromosome 1q and 1p, ring chromosomes 14 and 20, Phelan-McDermid syndrome (del22q13)) [Finsterer, J. *et al*., 2023].

Overall, the interesting study has some limitations and inconsistencies that call the results and their interpretation into question. Addressing these limitations would further strengthen and reinforce the statement of the study. Isolated and non-isolated genetic epilepsy presenting with tonic-clonic seizures carries the risk of SUDEP.

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